Rejections Under 35 U.S.C. § 112, first paragraph

1. Claims 1-12 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection.

The claims are drawn to protease inhibitors containing two or more transition-state isosteres, and a method of using such protease inhibitors to treat patients. Protease inhibitors having a single transition-state isostere are known. A transition-state isostere is a structure that mimics the transition state in the catalytic mechanism of proteases (Marciniszyn et al., 1976), *J. Biol. Chem.* 251:7088-7094) thereby providing the tight binding properties of the inhibitor (see specification, page 3, first full paragraph). Thus, the isostere is a structure with a non-cleavable bond that mimics the transition-state structure of the protease substrate (i.e. an amino acid chain). In other words, a transition-state isostere is a structure that is an analog of the transition-state of the peptide bond (and flanking amino acid structures) being cleaved by the protease.

The specification describes several transition-state isosteres suitable for use in the claimed protease inhibitors (see paragraph bridging pages 3 and 4, and page 12, lines 22-25, in the specification). These include hydroxyethelene, dihydroxyethelene, hydroxyethlamine, phosphinate, and reduced amide. Thus, applicants have provided specific description of representative (and preferred) transition-state isosteres. Such isosteres can be used in the disclosed protease inhibitors by simply incorporating them into a peptide or a peptide analog (where the peptide serves as a substrate analog for the protease to be inhibited). Applicants submit that those of skill in the art would have no trouble placing two or more isosteres in a

substrate analog (see also from page 11, line 25, to page 12, line 25). In view of information disclosed in the specification and knowledge of those of skill in the art, those of skill in the art would not have any trouble making the claimed protease inhibitors. The rejection provides no evidence and no reasoning to doubt this.

Applicants also submit that there is no problem in achieving inhibition with the claimed inhibitors. Inhibitors with a single transition-state isosteres are known. Their general mechanism of action is known. For the reasons discussed in the specification (and summarized below), inhibitors with two isosteres will not only function as inhibitors but will have useful characteristics that make them more effective. The position of the isostere (which is equivalent to that of the scissiled bond in the substrate) in the substrate analog peptide defines the subsite binding for the inhibitor residues.[1] That is, the transition-state isostere will bind to the protease at the active site (that is, with the isostere in the position of the bond normally cleaved by the protease). The claimed protease inhibitors, because they have two or more isosteres, will align in the substrate binding site in two (or more) different ways--one where each one of the isosteres is at the active site (see from page 9, line 8, to page 11, line 24). The result is that the substrate analog (i.e. the peptide or peptide analog containing the isosteres) presents different side chains for each different alignment, making it very unlikely that any one mutation (or even any few mutations) in the protease can prevent binding of the inhibitor. This effect is based on the

[1] Subsites are the portions of the substrate binding site that bind individual amino acid side chains.

presence of two or more isosteres in the inhibitor and is not subject to many unpredictable factors.

For all of the above reasons, applicants submit that it would not require undue experimentation for those of skill in the art to make and use the claimed protease inhibitors. For these reasons, applicants submit that the claims are fully enabled.

The rejection states that "it is not seen where the instant specification enables the ordinary artisan to determine what compounds would fit the instant claims." As discussed above, the specification provides clear guidance that can be easily followed to predictably arrive at numerous protease inhibitors as claimed. Protease inhibitors having one transition-state isostere were known. Various transition-state isosteres were known. Applicants have provided a sound framework and guidance for the use of two or more transition-state isosteres in a single inhibitor (see especially from page 11, line 25, to page 12, line 25). Applicants have provided an example of the claimed inhibitors that actually works as the specification describes. There is no evidence supporting the contention in the rejection that the specification fails to guide those of skill in the art. The rejection also concludes, without support, that it would require undue experimentation to make and use the claimed protease inhibitors. Applicants disagree and have provided reasons in the discussion above. Such an unsupported conclusion does not meet the burden on the Patent Office to establish that undue experimentation would be required. Thus, the rejection fails to make a prima facie case of lack of enablement. For this additional reason, applicants submit that the present rejection fails.

2. Claims 1-12 were rejected under 35 U.S.C. § 112, first paragraph, as not being adequately described in the specification. Applicants respectfully traverse this rejection.

As discussed above, the specification describes transition-state isosteres and their use in the claimed protease inhibitors. Transition-state isosteres are defined in the specification as structures that mimic the transition state in the catalytic mechanism of the protease (see page 4, lines 28-29). An isostere is a substance having a structure similar to another substance. A transition-state isostere is an isostere of the transition-state structure of the substrate. Those of skill in the art are aware of the structure and purpose of transition-state isosteres. As the specification makes clear, the transition-state isosteres for use in the claimed inhibitors are isosteres of the transition-state structures of the peptide bond that is cleaved in protease substrates. The specification provides examples and points out that such isosteres are known in the art (see paragraph bridging pages 3 and 4, and page 12, lines 22-25, in the specification). Examples include hydroxyethelene, dihydroxyethelene, hydroxyethlamine, phosphinate, and reduced amide. Applicants submit that the specification thus provides a sufficient description of the claimed protease inhibitors.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-12 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection.

Claims 1-12 were considered ambiguous in the use of the term "transition-state isosteres." As discussed above, transition-state isosteres are defined in the specification as

structures that mimic the transition state in the catalytic mechanism of the protease (see page 4, lines 28-29). An isostere is a substance having a structure similar to another substance. A transition-state isostere is an isostere of the transition-state structure of the substrate. As the specification makes clear, transition-state isosteres refer specifically to a structure that substitutes for a peptide bond and that has a structure similar to the transition-state of such a peptide bond during cleavage of the bond by a protease. The transition state of peptide bonds was known (see, for example, Figure 5 in Marciniszyn et al., *J. Biol. Chem.* 251(22):7088-7094 (1976)(of record)). The specification provides examples of transition-state isosteres of these peptide bonds (see discussions above) which makes the relationship between the transition state and the isosteres very apparent. It is not seen how the use of this term renders the claims ambiguous. In this regard, applicants note that there is no requirement that the exact structure of a claimed invention be recited in the claims. General terms having understandable meanings are permitted.

Claims 3 and 4 were considered ambiguous in the use of the term "aspartic acid protease." Applicants note that there is more than one aspartic acid protease. The aspartic acid proteases are a family of proteases that use a similar catalytic mechanism involving aspartic acid residues (see Figure 5 in Marciniszyn et al., *J. Biol. Chem.* 251(22):7088-7094 (1976)). The similarity in mechanism leads to a similarity in transition-state structure, which, in turn, leads to inhibition by a similar class of inhibitors. Thus, all of the protease inhibitors designed for aspartic acid protease are expected to inhibit all of the aspartic acid proteases. Thus, it is not seen how the use of this term renders the claims ambiguous.

Claims 5 and 11 were considered ambiguous in the use of the term "UIC-98-056." As the specification makes clear, UIC-98-056 refers to a particular chemical compound. The complete structure of the compound is shown in Figure 2. As can be seen, the full chemical name of this structure would be unwieldy and perhaps confusing. The molecular formula ($C_{44}H_{55}N_3O_9S$; also shown in Figure 2) does not uniquely define the compound. Many complex chemical compounds are given aliases to make it easier to describe them (e.g. aspartame and ibuprofen), even though such aliases do not describe the structure of the compounds except by association. It is also common to name chemical compounds using serial numbers (e.g. RU-486), again, even though such serial numbers do not describe the structure of the compounds except by association. Finally, applicants are allowed to be there own lexicographers. The claim term, UIC-98-056, is fully and clearly defined in the specification as referring to the chemical shown in Figure 2. Thus, there can be no ambiguity in the use of this term. Nothing in its use violates the requirements of 35 U.S.C. § 112, second paragraph.

Rejection Under 35 U.S.C. § 102

Claims 1-12 were rejected under 35 U.S.C. § 102(b) as being anticipated by Carroll et al., Bioorganic & Medicinal Chem. Letters 8:2315-2320 (1998) (Carroll (1)), Carroll et al., Bioorganic & Medicinal Chem. Letters 8:3203-3206 (1998) (Carroll (2)), or Baldwin et al., Structural Biol. 2(3):244-249 (1995). Applicants respectfully traverse this rejection.

The present claims require the presence of two or more transition-state isosteres in the protease inhibitors.

Carroll (1) discloses protease inhibitors having a single transition-state isostere (-CHOH-CH_2-). The compound in Table 1 where R4 is CH_3-CHOH-CH_2- (group 13) does not include two isosteres as alleged in the rejection. The terminal CH_3-CHOH-CH_2- would not function as a transition-state isostere since it lacks sufficient peptide structure on one side. Proteases cleave internal bonds in their peptide substrates. The terminal CH_3-CHOH-CH_2- structure in the compound of Carroll (1) would not serve as an isostere as required by the claims. Thus, Carroll (1) fails to disclose every feature of the claims. Accordingly, Carroll (1) fails to anticipate the present claims.

Carroll (2) discloses protease inhibitors having a single transition-state isostere (-CHOH-CH_2-). The C(O)NH groups identified in the rejection are not transition-state isosteres. Thus, Carroll (2) fails to disclose every feature of the claims. Accordingly, Carroll (2) fails to anticipate the present claims.

Baldwin discloses protease inhibitors having a single transition-state isostere (-CHOH-CH_2-). The CH(I-Pr)-C(O) groups identified in the rejection are not transition-state isosteres. Thus, Baldwin fails to disclose every feature of the claims. Accordingly, Baldwin fails to anticipate the present claims.

Allowance of claims 1-12 is respectfully solicited.

Respectfully submitted,

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I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Teresa R. Spratt

Date: January 8, 2001